07-12-05 AF/2881 IFW

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Applicant(s): **Whitehouse**

Docket No. **840.052.203**

Application No.	Filing Date	Examiner	Customer No.	Group Art Unit
09/901,428	**7/9/01**	**B. C. Anderson**	**04617**	**2881**

Invention: **MULTIPOLE ION GUIDE MASS SPECTROMETRY....**

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COMBINED TRANSMITTAL OF APPEAL BRIEF TO THE BOARD OF PATENT APPEALS AND INTERFERENCES & PETITION FOR EXTENSION OF TIME UNDER 37 C.F.R. 1.136(a) (Small Entity)	Docket No. 840.052.203

In Re Application Of: **Whitehouse**

Application No.	Filing Date	Examiner	Customer No.	Group Art Unit	Confirmation No.
09/901,428	7/9/01	B. C. Anderson	04617	2881	8546

Invention: **MULTIPOLE ION GUIDE MASS SPECTROMETRY......**

O I P E JC10 JUL 1 1 2005 PATENT & TRADEMARK OFFICE

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This is a combined Transmittal of Appeal Brief to the Board of Patent Appeals and Interferences and petition under the provisions of 37 CFR 1.136(a) to extend the period for filing an Appeal Brief.

Applicant(s) hereby request(s) an extension of time of (check desired time period):

☐ One month ☐ Two months ☒ Three months ☐ Four months ☐ Five months

from: **May 10, 2005** (*Date*) until: **July 10, 2005** (*Date*)

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01 FC:2253 510.00 OP

Fee for Appeal Brief:	$250.00
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COMBINED TRANSMITTAL OF APPEAL BRIEF TO THE BOARD OF PATENT APPEALS AND INTERFERENCES & PETITION FOR EXTENSION OF TIME UNDER 37 C.F.R. 1.136(a) (Small Entity)	Docket No. 840.052.203

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09/901,428	7/9/01	B. C. Anderson	04617	2881	8546

Invention: **MULTIPOLE ION GUIDE MASS SPECTROMETRY......**

TO THE COMMISSIONER FOR PATENTS:

This combined Transmittal of Appeal Brief to the Board of Patent Appeals and Interferences and petition for extension of time under 37 CFR 1.136(a) is respectfully submitted by the undersigned:

Signature

Dated: **July 11, 2005**

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Attorney Docket No. 840.052.203

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
C. M. Whitehouse

Art Unit: 2881

Serial No. 09/901,428

Examiner: B. C. Anderson

For: Multipole Ion Guide
Mass Spectrometry...

Filed : July 9, 2001

July 11, 2005

BRIEF ON APPEAL

Hon. Commissioner for Patents and Trademarks
PO Box 1450
Alexandria, VA 22313-1450

This brief is being submitted in triplicate to The Board of Patent Appeals and Interferences in support of the Applicant's appeal from the final rejection of the Examiner, having a mailing date of February 10, 2005, rejecting all pending claims 99 and 115.

A three month extension is requested herewith since July 10, 2005 fell on Sunday.

1. Real party in interest

Analytica of Branford, Inc.

2. Related Appeals and Interferences

None

3. Status of Claims

The rejection of claims 99 and 115 is appealed and are the only claims pending. Both claims are the subject of this appeal.

4. Status of Amendments

None.

5. Summary of invention

A method is claimed for performing MS/MS analysis of a sample ion population using a multipole ion guide in the ion path between an ion source and a Time-of-Flight (TOF) mass spectrometer. The multipole ion guide is capable of being operated in a mode whereby a range of ion mass-to charge (m/z) ratios may be selected, and/or in a mode whereby ions are trapped within the ion guide. The claimed method involves first selecting ions with a first m/z ratio as they are transmitted through and/or trapped in the ion guide by operating the ion guide in a m/z-selection mode. The m/z-selected ions (the 'parent' ions) are then subjected to collision-induced dissociation (CID) fragmentation in the ion guide to create fragment ions from the parent ions. The resulting fragment ions and any remaining parent ions are accumulated in the ion guide by operating the ion guide in trapping mode. A portion of the trapped ions are then released from the ion guide and are directed into the pulsing region of a TOF mass analyzer, where the released ions are then pulsed into the TOF mass analyzer and mass analyzed, thereby detecting the fragment ions which have m/z values different from that of the parent ions. A series of such TOF mass spectra are acquired by repeating the sequence of releasing another portion of trapped ions from the ion guide, and directing each portion, in turn, into the TOF mass analyzer pulsing region, and performing TOF mass analysis on each portion. With each repetition of this sequence, the time delay between the release of ions from the ion guide and the pulsing of these ions from the TOF pulsing region into the TOF mass analyzer is adjusted to improve the duty cycle efficiency for detection of the fragment ions.

6. Issues

The Examiner has rejected the claims because of inadequate support in the specification and Figures. Specifically, the Examiner states:

> "The drawings are objected to under 37 CFR 1.83(a). The drawings must show every feature of the invention specified in the claims. Therefore, **the first mass resolving spectrometer for selecting <u>parent ions having a first desired mass to charge ratio from an ion stream</u>; the means for subjecting <u>the selected parent ions having a first desired mass to charge ratio</u> to collision induced dissociation to generate fragment ions; means for <u>periodically releasing pulses</u> of the trapped ions into a Time-Of-Flight instrument to detect <u>ions with a second mass to charge ratio</u>; and means for <u>adjusting the delay to improve the duty cycle efficiency of ions with the second mass to charge ratio</u>** as recited in claims 99 and 115 must be shown or the feature(s) canceled from the claim(s)."
>
> ***
>
> "Claims 99 and 115 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.
>
> The specification is unclear for reciting the limitations "**the first mass resolving spectrometer for <u>selecting parent ions having a first desired mass to charge ratio from an ion stream</u>"; "the means for subjecting <u>the selected parent ions having a first desired mass to charge ratio</u> to collision induced dissociation to generate fragment ions"; "means for <u>periodically releasing pulses</u> of the trapped ions into a Time-Of-Flight instrument to detect <u>ions with a second mass to charge ratio"</u>; and "means for <u>adjusting the delay to improve the duty cycle efficiency of ions with the second mass to charge ratio</u>"** as recited in claims 99 and 115."

7. Grouping of claims

Claims 99 and 115 are grouped together for the argument.

8. Argument

The Examiner has refused to be persuaded by the additional arguments submitted to him May 19, 2004 to allow claim 99 of the present application. The claims 99 and 115 are sought to be approved to provoke an interference with U.S. Patent 6,285,027 (the '027 patent).

The Examiner states in the Office Action of August 17, 2004 that the specification is unclear for reciting various limitations in claims 99 and 115; that, in particular, the Examiner does not understand what devices are described for performing the steps of claims 99 and 115; and, hence, the Examiner contends that these limitations are not adequately disclosed in the specification.

Claim 99 reads:

1. A method of effecting mass analysis on an ion stream, the method comprising:

(a) passing the ion stream through a first mass resolving spectrometer, to select parent ions having a first desired mass-to-charge ratio;

(b) subjecting the parent ions to collision-induced dissociation to generate fragment ions;

(c) trapping the fragment ions and any remaining parent ions;

(d) periodically releasing pulses of the trapped ions into a time of flight instrument to detect ions with a second mass-to-charge ratio; and

(e) providing a delay between the release of the pulses of trapped ions and initiation of push-pull pulses in the time of flight instrument, and adjusting the delay to improve the duty cycle efficiency of ions with the second mass-to-charge ratio.

Response to Examiner's Rejection

Introduction to Response

First, this application is one of a series of related applications, all of which have been incorporated herein by reference. For ease of review prior patents are referenced by column and row where helpful in understanding the presentation herein. The list of related patents is attached as Exhibit A and the last three numbers are used as the reference numbers herein, i.e., 5,689,111 is '111.

The drawings were rejected to under 35 CFR 1.83(a). The Examiner stated that the drawings must show every feature of the inventions specified in the claims. It is respectfully submitted that the structure does show each and every feature of the claims. This will become more apparent in the argument submitted herewith identifying each and every detail in the specification supporting the claim limitations which the Examiner claimed were not supported. These limitations are identical to those which the Examiner suggests are not supported by the Figures. To the extent that the Examiner's position on the drawings involves incorporated by reference pre-existing issued patents in which no issue was ever raised about the drawings not supporting the functions described, it is believed the drawing objection is incorrect and inconsistent with the issuance of the prior patents in this series identified as Exhibit A.

One of ordinary skill in the art has sufficient information with the structure shown in the Figures and the methodology identified in the specification as to how to have the structure to produce the results and functions desired so that the drawings fully and completely identify each and every feature when taken in conjunction with the identified specification portions contained in the argument herein as well as those incorporated by reference in already issued prior patents.

Step (a) passing the ion stream through a first mass resolving spectrometer, to select parent ions having a first desired mass-to-charge ratio

"A. Support for step (a) 'passing the ion stream through a first mass resolving spectrometer, to select parent ions having a first desired mass-to-charge ratio', is contained in:

> Column 16, line 34, et seq.: "With the embodiment of the invention as diagrammed in FIG. 1, an MS/MS experiment includes the steps of m/z selection and accumulation in ion guide 16 operating in trapping mode followed by an ion fragmentation step. Initially, in an MS/MS experiment, the primary ion beam is turned on and ions enter ion guide 16 which is operating in m/z selection mode. As described above, mass or m/z selection in ion guide 16 can be achieved in a number of ways."

In other words, '...the primary ion beam is turned on and ions enter ion guide 16 which is operating in m/z selection mode...' in the '259 this is the same as the act of 'passing the ion stream through a first mass resolving spectrometer' of step (a). Also, the function part of step (a), 'to select parent ions having a first desired mass-to-charge ratio' is described by '...includes the steps of m/z selection'.

There appeared to be an issue during the interview with the Examiner in December, 2003, regarding the word 'through' in step (a). The first two definitions of the word 'through' in the Thorndike-Barnhart dictionary are: 1. from end to end of; from side to side of; between the parts of; from beginning to end of: march through a town, cut a tunnel through a mountain. 2. here and there in; over; around: stroll through the streets of a city. Taking the first definition of 'through' would imply that ions exit the mass spectrometer as part of step (a), while applying the second definition would imply that ions only need pass through a portion of the spectrometer as part of step (a), and need not exit. Hence, the meaning of the word through in step (a) covers both definitions (1) and (2) above literally and actually.

Interpretation of the word 'through' according to the second definition is an apt description of the function of step (a) of selecting parent ions. To 'select', that is, to chose to the exclusion of all others, ions with a particular m/z ratio need to be isolated, either spatially or temporally, from all others in any mass resolving spectrometer before the ions exit the spectrometer, if, in fact, the ions exit at all. This is well known in the art. In other words, exiting the mass spectrometer is not necessary for the 'selection' of ions of a particular mass-to-charge ratio. Therefore, the language of step (a) encompasses either situation of selecting 'parent ions having a first desired mass-to-charge ratio', that is: 1) passing the ion stream partly through or within the mass spectrometer and then allowing selected ions to exit; and 2) just passing the ion stream partly through the mass spectrometer. Step (a) does not require that ions go from end to end or completely through since the language is not so limited.

Nevertheless, the '259 patent description incorporated herein discloses different implementations of step (a) which support both interpretations of the word 'through'. In one approach disclosed in the '259 patent description, 'selected' ions do, in fact, exit the ion guide mass spectrometer prior to the next step of fragmentation, as described in Col. 17, lines 1-12:

> "...such that ions leaving ion guide exit 24 move to fill the gap between lenses 26 and 27. When the gap between lenses 26 and 27 is filled, the voltages on lenses 26 and 27 are rapidly increased effectively changing the energy of ions in the gap between the end of rods 20 and lens 27. The relative voltages on the lenses 26 and 27 and the offset potential of ion guide 20 are set such that the ions sitting at a raised potential are accelerated back into the exit end 24 of ion guide 16 and travel from ion guide exit end 24 toward ion guide entrance end 60 through the length of the internal volume of ion guide 16 colliding with neutral background molecules in a portion of the ion guide length."

Thus, selected ions exit the mass resolving spectrometer (ion guide) and are then accelerated back into the ion guide, which contains gas molecules with which the ions collide and fragment by CID. This process is identical to the description of mass selection and fragmentation given in '027, except that 'selected' ions having exited the mass resolving spectrometer are accelerated in the *downstream* direction to an ion guide with gas molecules to cause CID, while in '259, 'selected' ions having exited the mass resolving spectrometer are accelerated in the *upstream* direction to an ion guide with gas molecules to cause CID.

Alternatively, in another scenario, the '259 description discloses 'passing the ion stream through a first mass resolving spectrometer, to select parent ions having a first desired mass-to-charge ratio' without the selected ions having to exit the mass spectrometer before the next step of fragmentation takes place. This is described by the passage, Col. 16, lines 34-42, quoted in the beginning of this section A."

This passage from the '259 specification continues to explain three different ways that mass-to-charge selection may be performed with ion guide 16 in col. 16, lines 43-49:

> One is by setting the AC and DC voltage components on ion guide rods 20 resulting in operation near apex 100 stability diagram 102 in Fig. 9. A second method is by operating ion guide 16 along the a=0 line and applying resonant frequency rejection for all ions but the selected m/z value or values. A third method is to accumulate ions in RF only mode and by adjusting AC and DC amplitudes, scan out all but the m/z values of interest."

Furthermore, the sentence in col. 16, lines 38-40 "*Initially*, in an MS/MS experiment, *the primary ion beam is turned on and ions enter ion guide 16 which is operating in m/z selection mode.*", clearly distinguishes this mass-to-charge selection step as the <u>first</u> (initially) step in an MS/MS experiment.

The above quoted passages clearly disclose step (a), selecting parent ions having a first desired mass to charge ratio from an ion stream, and the device therefore used in the embodiment of Figure 1, to be the ion guide 16 which is operating in one of at least three different possible m/z selection modes, the requirements for which are described in the '259 specification, and which are well-known to those skilled in the art, as well.

Step (b) subjecting the parent ions to collision-induced dissociation to generate fragment ions

The May 19, 2004 Response states on page 8, line 32 through page 10, line 12 that:

> "B. Support for step (b), 'subjecting the parent ions to collision-induced dissociation to generate fragment ions', is also included in the above passage, specifically in lines 34-38 "...an MS/MS experiment includes the steps of m/z selection ... followed by an ion fragmentation step". Note explicit definition of the order of these steps. The ion fragmentation step is subsequently described in more detail in Col. 16, lines 53-67 and Col. 17, lines 1-12. First, Col. 16, lines 53-60 reads:
>
> > "Fragmentation of trapped ions in ion guide 16 can be achieved by using one of at least three techniques. The first technique as was described above for continuous beam operation is to apply a resonant frequency to rods 20 of ion guide 16 to cause resonant excitation of all or a portion of the trapped ions. The resonant excitation results in fragmentation due to CID of the translationally excited ions with the background gas in ion guide 16."

Because "Fragmentation of trapped ions in ion guide 16..." above refers to the m/z selected ions from step (a) which are then subjected to a fragmentation step, the trapped ions are the same as the 'parent ions' of the claims, step (b). Therefore, "Fragmentation of trapped ions in ion guide 16... of all or a portion of the trapped ions...due to CID of the translationally excited ions with the background gas in ion guide 16", in the '259 description, is the same as 'subjecting the parent ions to collision-induced dissociation to generate fragment ions' of step (b).

The above passage describes one embodiment of this step, that is, resonant frequency excitation fragmentation of parent ions while they are trapped in the ion guide. Obviously, any fragment ions so produced are also trapped in the ion guide.

A second method of achieving CID fragmentation of m/z selected parent ions is described in the immediately following passage, Col. 16, lines 61-67 through Col. 17, lines 1-12:

> "A second technique and another aspect of the invention allows higher energy fragmentation to occur than can be achieved with resonant frequency CID. This second ion fragmentation technique is realized by switching the offset potential of ion guide 16 and the voltage applied to lens 26 to release ions trapped in ion guide 16 and accelerating them at higher energy back into exit end 24. A short release pulse is used such that ions leaving ion guide exit 24 move to fill the gap between lenses 26 and 27. When the gap between lenses 26 and 27 is filled, the voltages on lenses 26 and 27 are rapidly increased effectively changing the energy of ions in the gap between the end of rods 20 and lens 27. The relative voltages on the lenses 26 and 27 and the offset potential of ion guide 20 are set such that the ions sitting at a raised potential are accelerated back into the exit end 24 of ion guide 16 and travel from ion guide exit end 24 toward ion guide entrance end 60 through the length of the internal volume of ion guide 16 colliding with neutral background molecules in a portion of the ion guide length."

Essentially, as described previously in section A., m/z selected parent ions are allowed to pass completely through the ion guide and out the exit end of the ion guide. Then, voltages applied to the exit lens components are switched such that the ions are turned around and accelerated back into the ion guide where they ultimately encounter gas molecules in the ion guide, and collisions with the gas molecules result in fragmentation of the ions by CID.

Thus, there appears to be ample support for step (b), as well as its proper order of execution, in the '259 description.

Further, regarding the order of execution of the steps of th claims: During the December 2003 interview with the examiner, a specific portion of the text in the '259 patent was pointed out to address his question of support for order of events as cited in the claim. The listed and numbered steps 1 through 8 in column 19, lines 55 through 67 and column 20, lines 1 and 2 describe in detail an MS/MS experiment with Trappulse TOF analysis conducted in the precise order as stated in the claims. The Examiner reviewed this passage during the interview with him and he raised no questions or objections.

Also during the interview with the Examiner, the examiner was focused on m/z selected parent ions being accelerated from one ion guide to a second ion guide to cause CID fragmentation. In column 21, lines 26 through 67 and column 22, lines 1 through 27 the description of the two ion guide embodiment diagrammed in Figure 4 is given where m/z ion selection occurs in ion guide 111 and m/z selected parent ions are reverse accelerated into ion guide 110 (column 22, lines 4 through 13) to cause ion collision induced fragmentation with both ion guides operating in trapping mode. The examiner accepted that the reverse accelerating ions from one ion guide to a second ion guide was a valid method of conducting CID and MS/MSn analysis creating the same fragment ion population as would result from forward acceleration of ions from one ion guide to a second ion guide with ion CID occurring in the second ion guide."

The above quoted passages refute this statement. This passage clearly identifies that step (b) 'subjecting the parent ions to collision-induced dissociation to generate fragment ions' is accomplished with ion guide 16 using one of two approaches to fragmentation. As described in the specification, ion guide 16 is the device used to perform step (b) in an ion fragmentation mode, subsequent to using the same ion guide 16 for performing step (a) in mass-to-charge selection mode. In other words, it is clear that

both step (a) and step (b) are performed using the same device, ion guide 16, but as is well known, they do so at different times and in different modes of operation. One of the two modes of fragmentation which uses ion guide 16 is also described to use additional devices, lenses 26 and 27 at the exit end of ion guide 16, to perform step (b).

> Step (d) periodically releasing pulses of the trapped ions into a time of flight instrument to <u>detect ions with a second mass-to-charge ratio</u>

"D. Support for step (d), 'periodically releasing pulses of the trapped ions into a time of flight instrument to detect ions with a second mass-to-charge ratio' is found in passages that immediately follow the latter quoted passage, that is, in Col. 17, lines 31-40:

> "After sufficient ion fragmentation has occurred by this method, a series of TOF mass spectra can be acquired of the ion population trapped in ion guide 16. As was described in an earlier section, releasing of trapped ions from ion guide 16 for TOF mass analysis followed by trapping of the ions remaining in ion guide 16, can be achieved either by changing the voltages on just lens 26 or conversely, the ion guide offset potential, skimmer 14 voltage and the voltage on capillary exit 12 can be stepped together."

This passage identifies that the next step after fragmentation and trapping is to acquire a series of TOF spectra of the ions trapped in the ion guide. The 'ions trapped in the ion guide' are obviously the fragment ions and any remaining parent ions from step (c). 'A series of TOF spectra can be acquired' (of these ions) identifies that this step (d) entails acquisition of a plurality ('a series') of TOF mass spectra of these ions, which, as is well known to those skilled in the art, inherently involves detection of ions with more than one mass-to-charge value, hence, certainly includes at least the detection of 'ions with a second mass-to-charge value' as specified in step (d). Further, 'releasing of trapped ions from ion guide 16 for TOF mass analysis followed by trapping of the ions remaining in ion guide 16' is the same as to 'periodically releasing pulses of the trapped ions into a time of

flight instrument', in step (d). This equivalence is more explicit in the detailed description in the earlier section referred to in this passage for the releasing of some trapped ions for TOF analysis and trapping of remaining ions. This earlier section is Col. 13, lines 3-67 through Col. 14, lines 1-29. Of particular relevance to step (d) is an excerpt from this passage, Col. 13, lines 62-66:

> "By either trapping method, ions continuously enter ion guide 16 even while packets are being pulsed out exit end 24. The time duration of the ion release from ion guide exit 24 will create an ion packet 52 of a given length as diagrammed in Fig. 2."

Hence, the '259 description describes packets (of ions) being released and pulsed out exit end 24 (of the ion guide trap), in other words, 'periodically releasing pulses of the trapped ions', as expressed in step (d). Therefore, support for step (d), 'periodically releasing pulses of the trapped ions into a time of flight instrument to detect ions with a second mass-to-charge ratio', in the '259 description, as well as for the sequence that step (d) follows step (c), is clear."

The first quoted passage of this section, that is, col. 17, lines 31-40 of the '259 specification, describes the devices/means for periodically releasing pulses of trapped ions into a TOF instrument to detect ions with a second mass-to-charge ratio: "releasing of trapped ions from ion guide 16 for TOF mass analysis ... can be achieved either by changing the voltages on just lens 26 or conversely, the ion guide offset potential, skimmer 14 voltage and the voltage on capillary exit 12 can be stepped together". This passage clearly describes that the voltage on lens 26 may be changed to release ions from ion guide 16 for TOF analysis. This is how the release is done as is well known.

An additional explicit description of the means for performing this step (d) is provided in the 'incorporated by reference' '111 patent, specifically col. 7, lines 22-31

(referring to the elements of Figures 1, 4 and 5 of the '111 specification:

> "As the voltage on the exit lens 15 is switched from level 78 to 77 for a short duration (of the order of microseconds), high density ion bunches are extracted collision free from the low pressure storage region 72 and injected into the orthogonal time-of flight analyzer. The mechanism for the storage mode of operation can be seen in FIG. 4. The ions are subsequently accelerated by means of additional electrodes 16 and 17. These electrodes in the present system are held at constant potentials, but they can be switched synchronously to the switching of the lens 15."

Step (e) providing a delay between the release of the pulses of trapped ions and initiation of push-pull pulses in the time of flight instrument, and adjusting the delay to improve the duty cycle <u>efficiency of ions with the second mass-to-charge ratio</u>

"E. Step (e) is 'providing a delay between the release of the pulses of trapped ions and initiation of push-pull pulses in the time of flight instrument, and adjusting the delay to improve the duty cycle efficiency of ions with the second mass-to-charge ratio'.

Again, ample support for this step is found in the '259 description and U.S. Patent Number 5,689,111 incorporated into '259 by reference. The 'push-pull' pulses refers the pulsed acceleration field that is turned on abruptly in order to accelerate ions in the TOF upon initiation of a TOF spectrum measurement. It is a term that is considered well-known to those familiar with the art of time-of-flight mass spectrometers. Indeed, the '027 specification uses this terminology without explanation or definition, for example, in Col. 5, lines 58-61: "Grids 36 are provided in known manner for effecting a push-pull pulse to ions collected in the ion storage zone 34.", and, in Col. 6, lines 35-37, "Line 74 shows the variation of potential of the conventional push-pull arrangement at the ion collection zone 34."

Support for step (e) is found initially in the '259 description in Col. 12, line 67 through Col. 13, lines 2:

> "Instead, trapping and the timed release of ions from the multipole ion guide is a preferred method for improving duty cycle."

This teaching introduces the concept of improving the duty cycle by a process of trapping ions and properly timing their release to the TOF. This concept is elaborated on, following a detailed discussion of different ways of performing the trapping step, in subsequent passage of Col. 13, lines 62-67 through Col. 14, lines 1-29:

> "By either trapping method, ions continuously enter ion guide 16 even while ion packets are being pulsed out exit end 24. The time duration of the ion release from ion guide exit 24 will create an ion packet 52 of a given length as diagrammed FIG. 2. As this ion packet moves through lenses 27 and into pulsing region 30 some m/z TOF partitioning can occur as diagrammed in FIG. 3. The m/z components of ion packet 52 can occupy different axial locations in pulsing region 30 such as separated ion packets 54 and 56 along the primary ion beam axis. Separation has occurred due to the velocity differences of ions of different m/z values having the same energy. The degree of m/z ion packet separation is in part a function of the initial pulse duration. The longer the time duration that ions are released from exit 24 of ion guide 16, the less m/z separation that will occur in pulsing region 30. All or a portion of ion packet 52 may fit into the sweet spot of pulsing region 30. Ions pulsed from the sweet spot in pulsing region 30 will impinge on the surface of detector 38. If desired, a reduced m/z range can be pulsed down flight tube 42 from pulsing region 30. This is accomplished by controlling the length of ion packet 52 and timing the release of ion packet 52 from ion guide 16 with the TOF pulse of lenses 34 and 35. A time separated m/z ion packet consisting of subpackets 54 and 56 just before the TOF ion pulse occurs is diagramed in FIG. 3. Ion subpacket 56 of lower m/z value has moved outside the sweet spot and will not hit the detector when accelerated down flight tube 42. Ion subpackets 57, originally subpackets 54, are shown just after the TOF ion pulse occurs. These subpackets will successfully impinge on detector 38. The longer the initial ion packet 52 the less mass range reduction can be

> achieved in pulsing region 30. With ion trapping in ion guide 16, high duty cycles can be achieved and some degree of m/z range control in TOF analysis can be achieved independent or complementary to mass range selection operation with ion guide 16."

This passage first describes a pulse, or packet, of ions of a given length (depending on the trap pulse duration) being pulsed out of the ion guide trap. Then, "As this ion packet moves through lenses 27 and into pulsing region 30 some m/z TOF partitioning can occur...". In other words, it takes some time for the pulsed ion packet to travel from the ion guide trap to the pulsing region of the TOF, and, obviously, the TOF push-pull pulse would not be activated until the ion packet, or some portion of the packet, has arrived within the TOF 'sweet spot', that is, the region within the TOF pulse region from which ions are able to reach the TOF detector once the TOF pulse occurs. This time delay is expressed explicitly in this passage by "...timing the release of ion packet 52 from ion guide 16 with the TOF pulse of lenses 34 and 35. A time separated m/z ion packet consisting of subpackets 54 and 56 just before the TOF ion pulse occurs is diagramed in FIG. 3." '...timing the release of ion packet...with the TOF pulse...' is the same as 'providing a delay between the trap release of the pulses of trapped ions and the initiation of push-pull pulses in the time of flight instrument' because timing release of individual packets inherently has a delay between successive individual packets. Such a delay is even more explicitly described in the '111 description, as discussed below.

The second part of step (e) is '...and adjusting the delay to improve the duty cycle efficiency of ions with the second mass-to-charge ratio'. The passage from '259 quoted above includes the statements: "All or a portion of ion packet 52 may fit into the sweet spot of pulsing region 30. Ions pulsed from the sweet spot in pulsing region 30

will impinge on the surface of detector 38." In other words, this passage teaches that all ions of an ion packet may be detected in the TOF, provided that they are located within the sweet spot of the TOF pulsing region at the time that the TOF pulse occurs. Now, as is known to one of skill in the art, all ions of an ion packet of a particular mass-to-charge ratio will be located within the sweet spot of the TOF pulsing region only if the timing of the TOF pulse occurs after a particular time delay relative to the ion guide trap release pulse. Hence, it would seem to be clear that this passage supports the second part of step (e) '... adjusting the delay to improve the duty cycle efficiency of ions with the second mass-to-charge ratio'.

The above arguments for support for step (e) in the '259 specification are further bolstered by considering the incorporation by reference of then co-pending patent application, now issued U.S. patent # 5,689,111, which describes in explicit detail the pulsed release of ions from an ion guide trap, and the improvement in duty cycle of an ion with a particular mass-to-charge ratio by adjusting the delay between the release of the pulses of trapped ions and initiation of TOF pulses. In the '111 description, Col. 8, lines 1-28 read:

> "As an example to the ion storage mode of operation, let us again use the same mixture of ions M1, M2, and M3 of ionic masses 997, 508 and 118 as used above in continuous mode of operation. As shown in FIG. 4, and FIG. 6 the pulsed ion beam of duration t1 from the region 72 is injected between the parallel plates 23 and 24 when the plates are initially held at the absence of an electric field, i.e. voltage level 79 on the repeller lens 23. According to the above equation (3), lighter ions moving faster than the heavier ions, the three masses will start to separate from each other in the region 26. After a certain variable delay t2, the electric field in the region 26 is pulsed on for a short period of time t3 by the repeller plate 23. The delay time t2 can be changed to allow different sections of the original ion beam, i.e. different m/z packages, to accelerate perpendicular to their original

> direction towards the flight tube 35 to be detected for mass analysis. In this example, a delay time t2 was chosen to pulse only a narrow range of ions centered around mass (M2) 53 which were accelerated in the direction 63 at the instant the field was turned on. At the same instant, both the masses M1 52 and M3 54 will hit the sides of the lenses moving in the approximate direction 62 and 64 and will not be detected by the mass analyzer."

This passage describes 'providing a delay (i.e., t2) between the release of the pulses of trapped ions and initiation of push-pull pulses in the time of flight instrument,' in the passage "After a certain variable delay t2, the electric field in the region 26 is pulsed on" , while 'and adjusting the delay to improve the duty cycle efficiency of ions with the second mass-to-charge ratio' is described by "..delay time t2 can be changed to allow.. different m/z packages.. to be detected for mass analysis.. a delay time t2 was chosen to pulse only a narrow range of ions centered around mass (M2) 53...". The resulting improvement in the duty cycle is demonstrated in the subsequent description of demonstrated experimental results in Col. 8, lines 44-67 through Col 9, lines 1-16, which read:

> "FIGS. 7A and 7B show the actual experimental results acquired using both the continuous and ion storage mode of operations for a sample using a mixture of ions used in the above examples. The actual sample was a mixture of three compounds Valine, tri-tyrosine, and hexa-tyrosine. Upon electrospray ionization of this mixture, the predominant molecular ions with nominal masses 118, 508, and 997 are generated in the ionization source 10. The bottom trace of FIG. 7A shows all three of these ions detected and registered as peaks 73, 71, and 74 when the mass spectrometer was in the continuous mode of operation. The top trace mass spectrum in FIG. 7A shows the results when the mass spectrometer was changed to the ion storage mode of operation. Both modes were acquired in similar experimental conditions. The acquisition rate i.e. the repetition rate counted by the repeller lens was 8200 per second. Each trace represents 4100 full averaged scans. As seen from the top spectral trace, there is only one

predominant registered peak 72 in the spectrum. This peak corresponds to a molecular ion 508 enhanced in signal strength by about a factor of ten with respect to the peak 71 in continuous mode of operation. For the reasons explained in above examples, both of the molecular ions 118 and 997 are absent from the ion storage mode spectral trace as expected. The signal intensity increase comes from the fact that all of the ions that would otherwise be lost in the continuous ion mode were actually being stored in the ion guide for the next scan. According to the above example, for the continuous mode of operation, the approximate duty cycle calculated for the 508 peak at 8,200 scans/s would be 9% i.e. one out of every twelve ions being detected. As the experimental results suggest in the ion storage mode of operation at 8,200 scans/s in FIG. 7A, most of the lost ions predicted in the continuous ion mode were recovered.

This passage demonstrates an a molecular ion 508 enhanced.. signal strength by about a factor of ten with respect to the peak 71 in continuous mode of operation... when the mass spectrometer was changed to the ion storage mode of operation, that is, as described in the previous passage, by providing a delay between the trap release and the TOF pulse, and adjusting the delay to maximize the intensity of the m/z 508 ion, resulting from an improvement in duty cycle relative to continuous beam operation.

Hence, there is sufficient support for step (e) in the '259 description only, and even stronger support when considering the included by reference description of '111."

While the explicit description of the method step (e) is discussed in detail in the May 19, 2004 Response, as reiterated above, the means for performing this method step (e) is further described explicitly in the '111 patent, col. 7, line 59 through col. 8 line 6:

"FIG. 6 shows the driving mechanism and the timing sequence between the ion guide exit lens 15 and the time-of-flight repeller lens 23 for a single cycle, i.e. a single mass spectral scan. The trace 83 shows the ion guide exit lens voltage status switching between the two voltage levels 77 and 78 and the trace 82 shows the repeller lens voltage

status switching between the two levels 79 and 80. The power supply 91 sets the desired upper and lower voltage levels to be delivered to the lenses at all times. The electrically isolated fast switching circuitry 92 controls synchronously the desired voltage levels of the lens electrode 15 and the repeller plate 23 to be switched back and forth during the designated time intervals controlled by the pulse and delay generating device 93, which is an accurate timing device, which in turn is controlled by the user interface."

In particular, this passage teaches explicitly that "a pulse and delay generating device 93 ... controlled by the user interface" is the means used to adjust the delay.

SUMMARY

Claims 99 and 115 are supported by the specification of this application Serial No. 09/901,428. Further, the support for the claims is unequivocally referenced by incorporation in the '259 patent by itself as well as by the inclusion of the '111 patent and other referenced patents incorporated therewith. As to the rejection of the Figures, it is submitted such rejection has also been overcome since the specification teaches one of ordinary skill in the art to operate the structure identified by reference numerals to achieve the steps of the method. Nothing more need be added to the drawings.

Respectfully submitted,

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CLAIMS ON APPEAL:

99. A method of effecting mass analysis on an ion stream, the method comprising:

(a) passing the ion stream through a first mass resolving spectrometer, to select parent ions having a first desired mass to charge ratio;

(b) subjecting the parent ions to collision induced dissociation to generate fragment ions;

(c) trapping the fragment ions and any remaining parent ions;

(d) periodically releasing pulses of the trapped ions into a Time-Of-Flight instrument to detect ions with a second mass to charge ratio; and

(e) providing a delay between the release of the pulses of trapped ions and initiation of pulses in the Time-Of-Flight instrument, and adjusting the delay to improve the duty cycle efficiency of ions with the second mass to charge ratio.

115. A method of effecting mass analysis on an ion stream, the method comprising:

(a) passing the ion stream through a first mass resolving spectrometer, to select parent ions having a first desired mass-to-charge ratio;

(b) subjecting the parent ions to collision-induced dissociation to generate fragment ions;

(c) trapping the fragment ions and any remaining parent ions;

(d) periodically releasing pulses of the trapped ions into a time of flight instrument to detect ions with a second mass-to-charge ratio; and

(e) providing a delay between the release of the pulses of trapped ions and initiation of push-pull pulses in the time of flight instrument, and adjusting the delay to improve the duty cycle efficiency of ions with the second mass-to-charge ratio.

APPENDIX

Exhibit A	Copy of first page of Filing Receipt and Copy of Additional Claims to Priority

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
09/901,428	07/09/2001	2881	472	840.052203	9	33	2

CONFIRMATION NO. 8546

UPDATED FILING RECEIPT

OC000000007011856

Levisohn, Lerner, Berger & Langsam
Suite 2400
757 Third Avenue
New York, NY 10017

Date Mailed: 11/02/2001

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

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Domestic Priority data as claimed by applicant

THIS APPLICATION IS A CON OF 09/676,124 09/29/2000
WHICH IS A CON OF 09/373,337 08/12/1999 PAT 6,188,066
WHICH IS A CON OF 08/794,970 02/05/1997 PAT 5,962,851
WHICH IS A CON OF 08/645,826 05/14/1996 PAT 5,652,427
WHICH IS A CON OF 08/202,505 02/28/1994 ABN
AND A CON OF 09/448,857 11/23/1999 ABN
WHICH IS A CON OF 08/971,521 11/17/1997 PAT 6,020,586
WHICH IS A CIP OF 08/689,459 08/09/1996 PAT 5,689,111 — '111
WHICH IS A CON OF 08/694,542 08/09/1996 PAT 6,011,259 * — '259
WHICH CLAIMS BENEFIT OF 60/002,117 08/10/1995
AND CLAIMS BENEFIT OF 60/002,118 08/10/1995
AND CLAIMS BENEFIT OF 60/002,122 08/10/1995
(*) Data inconsistent with PTO records.

Foreign Applications

If Required, Foreign Filing License Granted 08/08/2001

Projected Publication Date: Request for Non-Publication Acknowledged

Non-Publication Request: Yes

EXHIBIT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of:	Whitehouse et al.	**Patent Application**
Serial No.:	To be assigned	
Filing Date:	July 8, 2001	
For:	Multipole Ion Guide Mass Spectrometry with MS/MS^n Analysis	
Attorney Docket No.:	840.052.203	

Assistant Commissioner for Patents
Washington, D.C. 20231

Additional Claims to Priority

. . .which is a continuation of U.S. Patent Application Serial No. 08/645,826 filed May 14, 1996 (issued as U.S. Patent No. 5,652,427 on July 29, 1997), and which is a continuation of U.S. Patent Application Serial No. 08/202,505 filed February 28, 1994 (abandoned); and the priority of U.S. Patent Application Serial No. 09/448,857 filed November 23, 1999, which is a continuation of U.S. Patent Application Serial No. 08/971,521 filed November 17, 1997 (issued as U.S. Patent No. 6,020,586 on February 1, 2000) which is a continuation of U.S. Patent Application Serial No. 08/689,459 filed August 9, 1996 (issued as U.S. Patent No. 5,689,111 on November 18, 1997), and which claims the priority of U.S. Provisional Application Serial No. 60/002,118 filed August 10, 1995, and U.S. Provisional Application

Serial No. 60/002,122 filed August 10, 1995. The priority of all of the prior applications is claimed, and the disclosures of those applications are fully incorporated herein by reference.--

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